REMARKS

I. Status of the Claims

Upon entry of this Amendment, claim 21 will remain pending in the application. Claim 21 has been amended to recite a microorganism which is "*Escherichia coli* or yeast." Exemplary support for this amendment can be found in the specification at, for example, page 4, lines 8-15; page 6, lines 16-21; page 7, line 36, through page 8, line 2.

It is acknowledged that this amendment is submitted after final rejection of the claim. However, because the amendment places claim 21 in condition for allowance, or at least in better condition for appeal, entry thereof by the Examiner is respectfully requested.

II. Claim Rejections - 35 U.S.C. §112, First Paragraph

Claim 21 was rejected under 35 U.S.C. §112, first paragraph, for alleged lack of enablement. The Examiner asserted that there is no teaching in the specification regarding: (1) how to express *mutated* hPTH(1-84) in an intact form in any microorganism except yeast; and (2) what would be required to successfully express *intact and unmutated* hPTH(1-84) in "*any microorganism*" (emphasis added). Applicants respectfully disagree and request reconsideration and withdrawal of the rejection.

A. Contrary to the Examiner's Assertion, Claim 21 is not Directed to Mutated hPTH(1-84)

The Examiner asserted that there is no teaching in the specification regarding how to express *mutated* hPTH(1-84) in an intact form in any microorganism except yeast. Applicants note that claim 21 is *not* directed to *mutated* hPTH(1-84); rather, claim 21 is directed to a process for preparing "substantially pure recombinant hPTH."

B. Applicants' Claimed Invention is Enabled for Production of Intact and Pure hPTH in *E. Coli* or Yeast, as Recited in Amended Claim 21

As noted above, the Examiner asserted that Applicants' claimed invention is not enabled for expression of intact and pure hPTH in "any microorganism." While Applicants respectfully disagree with this ground for rejection, claim 21 has been amended to recite expression in "*Escherichia coli* or yeast," for the sole purpose of advancing the prosecution of this case.

The specification contains sufficient support to enable a person of ordinary skill in the art to produce "intact" hPTH (1-84) using the claimed invention, as amended. For example, on page 13, line 6, through page 14, line 14, construction of a genetically engineered microorganism that can produce exogenous and intact hPTH (1-84) is disclosed. The method is also exemplified in Example 8, where hPTH (1-84) is produced. The production of hPTH (1-84) is shown on an SDS-PAGE gel depicted in Figure 12. On page 34, lines 11-17, of the specification the gel is described as follows:

> Two major bands were seen in the medium from the pSSαL X 5-HPTH1 transformant that were not present in the medium from the pαL X 5 transformant: one band of approximately 9000 daltons, the expected size of hPTH, and one band of approximately 16000 daltons that could correspond to an unprocessed MFα1 -HPTH fusion product.

Therefore, a person of ordinary skill in the art, familiar with the disclosure of the priority document, would be able to produce intact hPTH (1-84) having the claimed properties, including the correct molecular weight, without undue experimentation.

Applicants' teaching is the first report of a recombinantly produced hPTH that is isolated in an intact form. While the prior art may have taught expression of the hPTH gene, prior art researchers were not successful in isolating hPTH in intact form from the production host. As argued in previous responses, prior art researchers were only capable of isolating hPTH fragments having some but not all characteristics of intact hPTH.

C. The Claimed Invention is Enabled for the Use of E. coli in the Claimed Process

As amended, claim 21 recites production of intact and pure hPTH in *E. coli* or yeast. Expression of intact and pure hPTH in *E. coli* is described in the application at, for example, page 7, lines 36-38 ("We have successfully expressed biologically active intact human parathyroid hormone as a secretory peptide in Escherichia coli . . ."). *See also* page 4, lines 1-8:

> there is provided by the present invention a novel plasmid for insertion in *E. coli*, containing DNA coding for human preproparathyroid hormone. The plasmid when inserted into *E. coli* functions to transform the *E. coli* such that the *E. coli* then produces multiple copies of the plasmid and thus of the cDNA coding for human preproparathyroid hormone.

(Emphasis added.) Finally, see page 5, lines 13-17 ("Additionally, the invention provides a downstream process technology for purification of human parathyroid hormone and derivatives. The process involves a purification procedure for yeast or E. coli medium or periplasmic solution . . .").

Because the claimed invention is enabled for production of hPTH in yeast and *E. coli*, withdrawal of this ground for rejection is respectfully requested.

III. Claim Rejections - 35 U.S.C. § 102(e)

Claim 21 was rejected under 35 U.S.C. § 102(e) as being allegedly anticipated by Kronenberg et al. (U.S. RE37919). Applicants respectfully traverse and request reconsideration and withdrawal of the rejection.

Kronenberg et al. is not prior art against the present application because the priority date of the present invention (October 22, 1986) is earlier than the filing date of Kronenberg et al. (May 4, 1994). The present application claims priority to U.S. Serial No. 06/921,684, filed on October 22, 1986. Exemplary support for claim 21 is found throughout U.S. Serial

No. 06/921,684. *See e.g.*, Example 8. Therefore, the rejection of claim 21 over Kronenberg et al. should be withdrawn.

CONCLUSION

As the above-presented amendments and remarks address and overcome all of the rejections presented by the examiner, withdrawal of the rejections and allowance of the claims are respectfully requested.

The Examiner is courteously requested to call the undersigned with any questions or comments regarding this response or the proposed amendments.

Respectfully submitted,

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Should additional fees be necessary in connection with the filing of this paper, or if a petition for extension of time is required for timely acceptance of same, the Commissioner is hereby authorized to charge Deposit Account No. 19-0741 for any such fees; and applicant(s) hereby petition for any needed extension of time.

MARKED UP COPY OF THE CLAIM

21. (Twice Amended) A process for the production of substantially pure recombinant hPTH, comprising the steps of:

(a) providing a microorganism that is engineered genetically to produce exogenous and intact hPTH(1-84), wherein said microorganism is selected from the group consisting of *Escherichia coli* and yeast;

(b) expressing said intact hPTH(1-84) within said microorganism; and

(c) purifying said intact hPTH(1-84) so as to produce an intact hPTH(1-84), wherein the intact hPTH(1-84) so produced: (1) reacts with antibodies against human PTH in a manner identical to the native hPTH(1-84) hormone, (2) has the molecular weight of the native hPTH(1-84) hormone, and (3) migrates as a single band when subjected to gel electrophoresis.